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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,869	11/29/2001	A. James Mixson	5627*6	9568

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	5

DATE MAILED: 05/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/036,869	MIXSON, A. JAMES	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An information disclosure statement and a preliminary amendment were received and entered as Paper Nos. 3 and 4, respectively, on 11/29/01. Claims 1-20 were canceled, and claims 21-35 were added as requested. Claims 21-35 are pending and under consideration in this Office Action.

Priority

This case is a continuation of 09/500,838, which is a continuation in part of 08/985,526, now abandoned, which is a continuation in part of 08/680,845, filed 12/5/97, now issued as US Patent 6,080,728. 08/985,526 provides no support for the instant invention which is directed to methods of inhibiting tumor growth through administration of RNA in a carrier which is either liposomes, cationic polymers, micelles, or combinations of these. Additionally, the '728 patent provides no support for delivering RNA by means other than a retrovirus. For these reasons, the priority date for the instant application is considered to be 2/10/00, the filing date of 09/500,838.

Claim Objections

Claims 21-35 are objected to because "lipsome" is misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 21-35 are drawn to methods of administering RNA to a subject for the purpose of inhibiting tumor growth or providing anti-angiogenic therapy. The RNA may encode any anti-angiogenic protein or peptide, and must be in a carrier which is a liposome, a cationic polymer, or a micelle, or a combination of these carriers. The specification lists preferred carriers at page 11, lines 26-28, and discloses retroviruses as an alternative to liposomes, cationic polymers, and micelles. The specification does not contemplate the delivery of retroviruses with liposomes, a cationic polymer, or a micelle carriers. For this reason, the scope of the term "RNA" in the claimed invention excludes RNA in retroviral particles, thus the claimed invention does not encompass the delivery of retroviruses.

The prior art taught that tumor growth could be inhibited by systemic and direct administration of DNA expression constructs encoding anti-angiogenic proteins or peptides. See US 6,080,728, claims 1-17. The specification asserts at page 4, lines 4-8 that the level of protein expressed from mRNAs delivered to cells by liposomal vectors is similar to that obtained from delivery of DNA, citing Malone et al (Proc. Nat. Acad. Sci. USA (1989)). However, a review of

Malone reveals no support for this assertion, as Malone does not report any comparison between RNA and DNA transfection. On the other hand, there are numerous reports indicating that mRNA delivery results in poorer gene expression than does DNA delivery. For example, Lu et al (1994) demonstrate that RNA/liposome transfection gave about 20-fold less expression per microgram of nucleic acid delivered than did DNA/liposome transfection. See Fig. 7 on page 251. Fisher et al (Biochem. J. (1997) 321:49-58) show that DNA/polylysine complexes gave expression efficiencies two orders of magnitude greater than the same mass of mRNA/polylysine complexes. Compare Fig. 7, panel C on page 55 with Fig. 8, panel C on page 56. Similarly, Conry et al (Cancer Research (1997) 55: 1397-1400 shows that injection of equal masses of mRNA and DNA into mouse tongue muscle in vivo resulted in nearly two orders of magnitude greater expression for DNA over RNA. See Fig. 3 on page 1399. Furthermore, the proponents of mRNA transfection teach that this process is best suited for situations which require only transient expression of the protein of interest. See Malone (Focus (1998), page 65, column 2, lines 6-10; Dwarki et al (1993), page 654, first full paragraph, and Conry et al (1997), page 1397, column 2, lines 20-26, and Fig. 3 on page 1399. Such applications could include immunization.

The prior art teaches the delivery of mRNA *in vivo* for the purpose of stimulating an immune response against an antigen encoded by the mRNA. See e.g. Martinon et al (Eur. J. Immunol. (1993) 23: 1719-1722). However, a search of the prior art did not reveal any therapeutic immune responses induced by mRNA transfection, nor the use of mRNA transfection for any other therapeutic purpose. In fact, after the invention was filed it was noted that there are

very few examples of attempted use of RNA in the field of gene therapy, due to the instability of delivered RNA, and the difficulty in working with RNA relative to plasmid DNA.. See Bettinger et al (Nucl. Acids. Res. (2001) 29(18): 3882-3891, page 3882, lines 1-7. Indeed, at the time the invention was made, successful implementation of nucleic acid-mediated therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). Given that the major problems facing gene therapy in general are related to poor gene expression, and that the art teaches that gene expression from

DNA transfection is generally greater and longer lasting than that obtainable from RNA transfection, one of skill in the art would not have expected that the claimed invention could be operational without some improvement in the state of the art.

Guidance in the specification regarding RNA transfection is essentially absent, being limited to two brief passages at page 4, lines 4-8, and page 19, lines 4-7. No specific guidance is given concerning the delivery of RNAs using the compositions and methods of the invention. For example, Applicant has failed to teach how to compensate for the fact that mRNAs are not replicated *in vivo*, and are much less stable than DNAs, whereas a single expression vector can give rise to a large number of mRNAs over a period of days or weeks. The specification fails to address methods for increasing the stability of RNA for purposes of transfection and expression *in vivo*. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the

> art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the specification entirely omits any guidance as to the amounts of specific RNAs which would be required to practice the methods, the amounts of carriers which are appropriate for each mRNA, or the appropriate modifications for increasing the stability and expression of RNA in vivo. Given the unpredictability of gene therapy in general, the absence of examples of therapeutic RNA delivery in the specification or the prior art, and the failure of the specification to provide any guidance whatsoever as to how to improve the stability and expression of delivered RNAs, one of skill in the art would have to perform undue experimentation in order to practice the claimed methods.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 21-35, the phrase "such carriers" renders the claim indefinite because it is unclear what are the metes and bounds of this phrase. More specifically, it is unclear whether

"such carriers" encompasses only liposomes, cationic polymers, and micelles, or whether it encompasses other carriers disclosed in the specification.

Claim 22 is indefinite because it recites the "the injection" without antecedent basis.

Claim 28 is indefinite because it recites "the tumor" without antecedent basis.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER